

Appl. No. 09/852,547
Amdt. Dated October 4, 2005
Reply to Office Action of May 4, 2005

REMARKS/ARGUMENT

Status of Claims

Claims 1-8, 12-15, 17-20, 66-69, 71, 73-79 and 81-89 and 92-94 were rejected.

Rejections Under 35 U.S.C. § 112, First Paragraph.

In the Office Action, claims 1-6, 12, 17-19, 66, 67, 70-73-76, 81-86 and 89 are rejected under 35 U.S.C. § 112, first paragraph for lack of enablement.

Applicant respectfully traverses the rejection. The Action in numbered paragraph "3," pages 2 -6 describes in great detail the many contradictory references in the art that are overcome by the present invention. The Action summarizes numerous references that were gathered based on the elements and/or limitations that are claimed by the present invention to form an enablement rejection, however, it is the present specification that, for the first time, recognizes the problem in the art and solves the problem, namely, a comprehensive solution to the problem of predicting susceptibility of a mammalian subject to development or growth of a steroid hormone responsive cancer in a mucosal epithelial tissue. While the action sets forth the many reasons that a skilled artisan may "reasonably conclude" or find it "reasonable to conclude" the present invention, it does so based on impermissible hindsight.

As regards enablement, the Applicant agrees with the Action to the extent that the art had been unpredictable, until the present disclosure focused for the first time the inquiry into the exact elements necessary to predict disease progression.

The law in this matter is simple, as long as the Applicant provides the manner of making and using the invention in terms amenable to those of skill in the art it complies with the enablement requirement of the first paragraph of §112. The exception to enablement is if there is reason to "doubt the objective truth of the statements contained therein which must be relied on for enabling support." *Fiers v. Sugano*, 984 F.2d 1164, 25 U.S.P.Q.2d 1601 (Fed. Cir. 1993). That is not the case here. Clearly, the Applicant has provided sufficient examples, figures and data to support the present claims, including Examples 22 and 23. The Action assembles disparate references that fail to cast doubt as to the "objective truth" of the matter asserted and claimed. Applicant's respectfully request that the Examiner file an affidavit for the record to support her doubt or withdraw the rejection.

An adequate written description of the invention may be shown by any description of sufficient, relevant, identifying characteristics so long as a person skilled in the art would recognize that the inventor had possession of the claimed invention. See, e.g., *Purdue Pharma L.P. v. Faulding Inc.*,

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230 F.3d 1320, 1323, 56 USPQ2d 1481, 1483 (Fed. Cir. 2000). Clearly, the Applicant has described with sufficient detail the relevant, identifying characteristics of the invention as claimed. At best, the Action demonstrates that the art is complex, however, given the relatively high level of skill of the Applicant, as shown in the present specification, the invention is described with sufficient detail to support a claim to showing the details of a method for predicting susceptibility of a subject to the development or growth of a steroid hormone responsive cancer in a mucosal epithelial tissue, as shown by the extensive survey of known cancers summarized in Table 1. The method of quantitating and/or detecting dimeric/polymeric IgA, polymeric IgM and IgG1 from a body fluid or secretion obtained from a subject is well known. Those observations, coupled with the demonstration that the inhibition of steroid hormone responsive cell growth can be reversed by a steroid hormone and its correlation with dimeric/polymeric IgA, polymeric IgM and IgG1 is clearly taught. The specification clearly teaches the artisan that the inhibition of steroid hormone responsive cell growth in the tissue is predictive of increased susceptibility to development or growth of a steroid hormone responsive cancer in a mucosal epithelial tissue.

As regards paragraph 4 under the Section 112, first paragraph rejection, the Applicant respectfully traverses the rejection. As the rejection does not specify a claim to which it is drawn, the Applicant nevertheless responds to the assertion made by the examiner. The Action makes a teleological argument based on the knowledge gathered from the present specification, namely, that the design of the experiment is predetermined from the base conditions of, e.g., levels of serum immunoglobulin controlling the extent of IgA available for transcytosis based on a surplus of secretory component. The Action provides no cite or reference that indicates that this is the case in a mucosal cancer. Applicant again request that the examiner place that evidence in an affidavit of record or withdraw the rejection. Regardless of the assertions of serum IgA as the limiting component in mucosal secretions, the skilled immunologist knows that the level and secretion of immunoglobulins such as IgA, the extent of Th1 versus Th2 cell activation, the processing and presentation of antigens on MHC to T cells and the activation of B cells are complex interactions that depend on the antigen, the host and the type of immune response. The present specification teaches, for the first time, that it is in this unique microenvironment that the correlation and predictability can be made. The Action includes no evidence to rebut the findings herein using the cells and conditions taught to the skilled artisan, and claimed herein. If the Action rejects the

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claims based on the examiner's doubt, the Applicant respectfully request that the Examiner file an affidavit for the record to support her doubt or withdraw the rejection.

Rejection under 35 U.S.C. § 112, first paragraph, for failing to comply with the written description, inadequate description of a genus.

Next, the Action rejects claims 7, 8, 13, 14, 17, 19, 20, 67, 68, 69, 77-79, 88, 91 and 93 under 35 U.S.C. § 112, first paragraph, for failing to comply with the written description. The action states that there is an inadequate description of a genus. A genus/species relationship is a highly subjective determination, more properly addressed with a restriction requirement. Regardless, the Applicant respectfully traverses this rejection. The skilled artisan will easily recognize what is meant by, and the scope of, a poly Ig receptor. Poly Ig receptors are a clearly recognized category, namely, receptors that are specific for immunoglobulins, as clearly taught in the specification.

The law as regards written description is clear, what is well-known is best omitted. In re Buchner, 929 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991). All that is necessary is that one skilled in the art be able to practice the claimed invention, given the level of knowledge and skill in the art. Further the scope of enablement must only bear a "reasonable correlation" to the scope of the claims. See, e.g., In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

In this case, the skilled artisan could easily assemble and engineer even a mutant version of the poly Ig receptor given minimal skills as a molecular biologist. Poly Ig receptors have been made and engineered for a dozen years or more as both soluble and secreted forms. There is no requirement in the law or scientifically for each and every single sequence variant to be disclosed as those sequences and structures are well-known in the art.

Lilly and Enzo are inapplicable in this situation. Those cases related to new, unknown DNA sequences for which little or no structural data was available. In this case, poly Ig receptors have been known for well over a decade, in fact, simple immunology textbooks such as Immuno Biology, The Immune System in Health and Disease, Janeway, et al., Garland Press, NY, (1999) at 326, teach about poly Ig. Janeway even includes a three-dimensional structure for the related FcRn receptor for IgG. All of these poly Ig receptors are closely related to MHC, which itself contains Ig-like domains. All this is well-known to the skilled immunologist. Furthermore, Poly Ig receptors are clearly discussed in Example 22.

Returning to Enzo and Lilly, these are also inapplicable as related to steroid hormone, poly Ig receptors and defective forms of the same. These cases address issues of fact under which a new

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gene sequence was being discovered, not well-known and characterized receptors. In fact, under Enzo and Lilly, the opposite finding would be made as to these particular receptors as taught and claimed in the specification. As taught in the specification:

[0434] Structural Properties of the Poly-Ig Receptor. The negative response to IgA and IgM is mediated by the mucosal poly-Ig receptor or a very similar structure with the same immunoglobulins specificity as well as the same immunological and M_r properties. The poly-Ig receptor is a M_r 100,000 transmembrane protein with several properties that place it in the Ig superfamily of receptors (Krajči P *et al.* (1992) *Eur J Immunol* 22, 2309-2315; Williams AF and Barclay AN (1988) *Annu Rev Immunol* 6, 381-405). The poly-Ig receptor and the secretory component from human has been cDNA cloned and DNA sequenced (Krajči P *et al.* (1992) *Eur J Immunol* 22, 2309-2315; Krajči P *et al.* (1995) *Adv Exp Med Biol* 371A, 617-623; Krajči P *et al.* (1991) *Hum Genet* 87, 642-648; Krajči P *et al.* (1989) *Biochem Biophys Res Commun* 237, 9-20) as has the poly-Ig receptor from mouse (Kushiro A and Sato T (1997) *Gene* 204, 277-282; Piskurich JF *et al.* (1995) and bovine tissue (Verbeet MP *et al.* (1995) *Gene* 164, 329-333). Altogether, the human poly-Ig receptor coding sequence encompassed 11 exons. The extracellular five domains originate from exons 3 (D1), exon 4 (D2) exon 5 (D3 and D4), exon 6 (D5), exon 7 (the conserved cleavage site to form the secretory component), exon 8 (the membrane spanning domain), exon 9 (a serine residue required for transcytosis), exon 9 (sequence to avoid degradation), exon 10, no known function) and exon 11 (sequence contains a threonine residue and the COOH terminus) (Krajči P *et al.* (1992) *Eur J Immunol* 22, 2309-2315).

The specification clearly teaches much about what is well known in the art about these receptors. As such, the Applicant respectfully request withdrawal of the written description rejection.

Rejection under 35 U.S.C. § 112, first paragraph, New Matter.

Next, the Action rejects claims 7, 19, 20, 77-79, 86 and 93 under 37 U.S.C. § 112, first paragraph, for New Matter. As regards "cancerous and pre-cancerous" conditions, the language may be found in claim 17 as filed, which is part of the specification. As regards "reduced prognosis" the language may be found in claim 19, as originally filed.

As regards the language related to "estrogen-based therapy" and "contra-indication of estrogen-based" therapy this is clearly within the scope of the present invention. While the language may not be found *ipsis verbis* within the specification, it is clear that the entire thrust and refinement of the present invention relates directly to this scientific point, namely, that therapy for mucosal cancers may be improved based on an understanding of the basis for disease. Consistent with current case law as represented by *Fujikawa v. Wattanasin*, 93 F. 3d 1559, 39 USPQ2d 1895 (Fed. Cir. 1996): *Ipsis verbis* disclosure is not necessary to satisfy the written description requirement of section 112. Instead, the disclosure need only reasonably convey to persons skilled in the art that the inventor had possession of the subject matter in question.

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The Summary of the Invention addresses squarely this proposition within the specification, namely, the importance of the determination of the responsiveness of the cancer to hormonal therapy as such:

[0018] In accordance with certain embodiments of the present invention, methods of assessing risk or susceptibility of an individual to developing a neoplastic lesion or cancerous tumor of a mucosal epithelial tissue are provided. In some embodiments the method includes detecting, and in some cases also quantitating, a steroid hormone reversible immunoglobulin inhibitor of steroid hormone responsive cell growth in a body fluid or secretion obtained from said subject, such as serum, plasma, colostrum, breast aspirates, saliva, tears, bronchial secretions, nasal mucosa, prostatic fluid, urine, semen or seminal fluid, vaginal secretions, ovarian aspirates, stool, and mucous secretions from the small intestine or stomach. The absence or deficiency of the immunoglobulin inhibitor compared to a predetermined standard material indicates or suggests that a steroid hormone responsive mucosal epithelial tissue in the body of the individual is secreting or bathed by less than a cell growth inhibitory amount of the immunoglobulin inhibitor. For the purposes of this disclosure, the term "immunoglobulin inhibitor" refers to a secretory immunoglobulin, preferably one or more of the secretory immunoglobulins IgA, IgM and IgG1, that is active for inhibiting proliferation of a steroid hormone responsive cancer cell maintained in a suitable nutrient medium under cell growth promoting conditions, in the absence of an inhibition-reversing amount of the steroid hormone or other substance that mimics this steroid hormone effect. The immunoglobulin inhibitory activity, also referred to as immunoglobulin inhibition, is distinct from any additional antigen-antibody recognition based immunological functions of the immunoglobulin inhibitors. The term "steroid hormone reversible immunoglobulin inhibitor" refers to the characteristic of the preferred immunoglobulin inhibitors that their cell growth inhibitory activity is steroid hormone reversible. "Cell growth promoting conditions" refer to favorable environmental conditions, other than defined medium components, and include such things as gaseous environment, humidity, temperature, pH, and the like. For example, cell growth promoting conditions could include incubation at 37°C in a humid atmosphere of 5% (v/v) CO₂ and 95% (v/v) air in a defined nutrient medium at pH 7.4. (emphasis added).

As regards the language "the ability of said poly Ig..." is clearly taught in Examples 22 and 23. Applicant respectfully request withdrawal of these rejections.

Rejections Under 35 U.S.C. § 112, First Paragraph, lack of enablement for non-functional receptors.

Claims 8, 67, 68 and 91 are rejected under 35 U.S.C. § 112, First Paragraph for lack of enablement. Applicant respectfully traverses the rejection and incorporated herein by reference the argument made, supra, as relates to poly Ig receptors. The Applicant does not see the language "non-functional" receptors in the claims rejected. Applicant respectfully request that the language or similar scope be identified or the rejected withdrawn.

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Rejection in Paragraph 7.

Applicant assumes that the rejection of claims 7, 12, in part, 13-15, 17 in part, 18 in part, 19, 69, 71 and 92 for method of detecting loss fall under 35 U.S.C. § 112. In response, the Applicant points out that the key observation in support of the present invention may have nothing to do with mutant receptors and the like. There is no requirement at law that the applicant know, in fact, the exact structures and/or mechanisms that underlie critical observations. In fact, any number of factors, including genes, promoters, gene expression, post-translational modifications, second messenger signals and the like, that are known and unknown may be involved in the underlying mechanism that supports the present invention. The proper inquiry is whether the Applicant places a full and operative invention in the hands of the skilled artisan. Regardless of the actual underlying mechanism, the Applicant teaches, enables and provides sufficient written description in the examples to support the claims and the invention. The inquiry is not whether the skilled artisan knows the mechanism of action (i.e., which receptor, if any, is defective) but rather, if the claims are supported. What is enabled and taught is what is claimed, viz., the observation that quantitating and correlating the immunoglobulin inhibitor to steroid responsive mucosal cancers. Applicant respectfully request withdrawal of the rejection.

Rejection Under 35 U.S.C. §102, under Harris, et al. "as evidenced by" Cargo, et al.

Claims 8, 67 and 91 are rejected under 35 U.S.C. §102, under Harris, et al. "as evidenced by" Cargo, et al. Anticipation requires that each and every element of a claimed invention be disclosed in a single reference. Applicant knows of no such "evidenced by" rejection. Applicant respectfully request withdrawal of the "evidenced by" rejection or support the same with statutory language and/or case law in support of the same.

Regardless, the Applicant traverses the rejection. Nothing in Harris teaches a correlation between a cancer and the immunoglobulin inhibitor of the present invention as found in a specimen. Applicant requests that the exact language of the referenced art be cited with particularity of the rejection be withdrawn.

Numbered Paragraph 9. Applicant does not understand the nature of numbered paragraph 9. For the record, Applicant traverses the argument that "nothing" teaches the exact molecular weight or partial amino acid sequence of a particular species of an inhibitor. In fact, no such protein may exist. Furthermore, no such teaching of a mechanism, sequence and/or molecular weight is required under the law. All that is required is that the skilled artisan be able to make and use the

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invention based on the written description. The legal standard is not whether an actual amino acid sequence is known. In fact, there may be none. The mechanism may be post-translation, caused by lipid metabolism, carbohydrate additions, inhibitors of DNA binding, or any of a number of other biological factors. Those are irrelevant to the inquiry at hand. The Applicant has taught how to identify the factors (from a specimen), how to measure them (cell proliferation), how to overcome the inhibition (addition of steroids), etc. Without question, how to obtain the factors, how to evaluate their activity, how to measure them, etc., are taught in the specification as filed and in the claims as drafted.

Applicant acknowledges and welcomes the withdrawal of prior rejections and objections in keeping with the principle of compact prosecution. Applicant's new counsel attempted to contact the examiner but received no response. Applicant's counsel looks forward to the opportunity to discuss any optional language that will advance the prosecution of this application.

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Conclusion

In light of the amendments, remarks and arguments presented above, Applicants respectfully submit that the claims in the Application are in condition for allowance. Favorable consideration and allowance of the pending Claims 24, 26-30 and 40-50 and new claims 52 and 53 are therefore respectfully requested.

If the Examiner has any questions or comments, or if further clarification is required, it is requested that the Examiner contact the undersigned at the telephone number listed below.

Dated: September 28, 2005.

Respectfully submitted,

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